ORIGINAL RESEARCH

Maternal Serum Anti-Müllerian Hormone Levels as Predictor of Preeclampsia

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Abstract

Aim: This study aims at finding the association of serum anti-Müllerian hormone (AMH) levels at 11–14 weeks of gestation in the prediction of preeclampsia.

Materials and methods: Antenatal patients between 11 and 14 weeks of gestation were recruited after providing written informed consent. Serum AMH was done for all patients. They were then categorized into the low AMH group and the normal AMH group. They were followed for the development of preeclampsia till 7 days postpartum and the pregnancy outcomes of both groups were compared.

Conclusion: The occurrence of preeclampsia in patients with normal AMH levels was low accounting for 34.4% compared to patients with low AMH levels where preeclampsia was 65.6%. The occurrence of preeclampsia at a tertiary care hospital was 16.6%. The frequency of preeclampsia in patients with low AMH was 9 times higher than normal AMH levels. Thus, low AMH levels at 11–14 weeks can predict preeclampsia so should be incorporated into first-trimester screening.

Clinical significance: Biomarker maternal serum AMH has recently been related to preeclampsia and its connection with the placenta and heart muscle would suggest its role in preeclampsia and cardiovascular risk later in the life of women with low AMH levels.

Keywords: Gestational age**,** Preeclampsia, Serum anti-Müllerian hormone.

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Introduction

High blood pressure episodes in pregnancy are associated with increased incidence of maternal and newborn mortality and morbidity.[1] The second and third most common causes of maternal mortality and morbidity around the world, respectively, are eclampsia and preeclampsia.[2] In India, 8–10% of pregnant women are estimated to have preeclampsia.[3] The second biggest cause of maternal mortality (14%), after hemorrhage is hypertensive disorders, notably preeclampsia.[4,5] Several factors, including genetic, vascular, immunological, and oxidative stress, have been hypothesized in the etiology of preeclampsia, but the results have been varied and conflicting.

A biomarker called maternal serum anti-Müllerian hormone (AMH) has recently been related to preeclampsia. Granulosa cells in the ovary generate the glycosylated glycoprotein known as AMH.[6,7] During pregnancy, AMH levels decrease as the pregnancy advances, then rise again after delivery.[7]

Anti-Müllerian hormone levels should be examined in expectant women between 11 and 14 weeks of gestation since though the levels of AMH are low throughout pregnancy due to high estrogen levels, and as pregnancy advances AMH levels decrease further till the end of pregnancy to be in minute amounts and then start rising after delivery.[8] So, the time of gestation of 11–14 weeks is when AMH levels are better read.

Preeclampsia patients showed lower serum AMH levels than normal blood pressure patients The presence of AMH receptors on the placenta and cardiac tissues implies that vascular complications associated with preeclampsia may impact ovarian ageing, raising cardiovascular risk in preeclamptic women later in life.[9,10] Some researchers discovered that biomarker serum AMH levels in prenatal preeclamptic women were found to be lower than in normal blood pressure women at 11–14 weeks of gestation.[8–11] Whereas some studies showed no association[12,13] between AMH and emergence of preeclampsia. Preeclampsia is intricate, and till date no clinically useful test can be applied to predict preeclampsia.

Reducing morbidity and mortality among pregnant women and their babies as a result of hypertension illnesses should be a clinician's primary priority. Preeclampsia and other long-term cardiovascular risks can be avoided by knowing the function of AMH in pathophysiology, which will be aided by this study. There is a paucity of Indian research establishing a link between AMH levels and preeclampsia. As a result, this study was carried out finding the association of serum AMH hormone levels at 11–14 weeks of gestation in prediction of preeclampsia. The study aims at finding the association of serum AMH levels at 11–14 weeks of gestation in prediction of preeclampsia and compare the maternal and perinatal outcomes in low AMH and normal AMH patients.

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Materials and Methods

This is a prospective observational study carried out at a rural based tertiary care institute. Ethical clearance for the study was obtained from the Ethical Review Committee of Datta Meghe University of Medical Sciences, Wardha, Maharashtra, India (IEC/2020-21/9341). The incidence of preeclampsia in the geographic region of study site is found to be in the range of 16.6%.

Sample size formula with desired error of margin 4% is as follows:

$$n = Z_{\alpha/2}{}^2 \times p \times (1 - p)$$

The sample size calculated was 350.

Written informed consent was taken in the local language, data collection was done with help of a predesigned, pretested, structured proforma. Information pertaining to history taking, examination and ultrasonography was entered in the tool.

The inclusion criteria included antenatal women with gestational ages ranging from 11 to 14 weeks, willing to enroll in the study with singleton pregnancy, and spontaneous conception.

The exclusion criteria included systemic illnesses (cardiovascular disease, renal disease, immunological disease, endocrinological disease, and diabetic mellitus); a history of preeclampsia, abortion, and intrauterine fetal death; multiple pregnancies; hydatidiform mole; artificial reproductive techniques; obesity; gestation below 11 weeks or above 14 weeks. According to the selection criteria, 350 women between 11 and 14 weeks of gestation were chosen as participants.

Sociodemographic particulars of patients were noted. Obstetric history including gravida, para, abortions, menstrual history including regularity of menstrual cycles, history of hypertensive disorders, diabetes mellitus, thyroid disorders, autoimmune illnesses, prematurity, intrauterine growth restriction, previous neonatal deaths were asked. We inquired about any specific surgery history, family history, and nutrition history. Women's gestational age was determined by their previous menstrual period, menstrual cycle regularity, clinical examination, and/or an early ultrasound scan.

On general examination, weight, height, pulse, blood pressure, pallor, pedal oedema, icterus, clubbing, lymphadenopathy, breast, and thyroid examination were noted. Following the standards for measuring blood pressure, BP was recorded at each visit and mean arterial blood pressure (MABP) was calculated throughout pregnancy.

Systemic examination, obstetrical examination for clinical gestational age, lie of fetus, presentation, presenting part, and amount of liquor was noted, and fetal heart sounds (FHS) were auscultated with stethoscope.

Antenatal investigations, namely, HIV, hepatitis B surface antigen (HbSAg), venereal disease research laboratory (VDRL) tests; blood group; complete blood count with peripheral smear; thyroid profile; blood glucose levels; and urine were tested for sugar, albumin, and pus cells.

At 11–14 weeks of gestation maternal serum AMH level was tested. Normal AMH levels in the first trimester range from 1.54 ng/mL to 2.66 ng/mL.[8] Anti-Müllerian hormone levels were considered low in patients with values less than 1.54 ng/mL.

Categorization

- Group I: Antenatal women with normal serum AMH levels.
- Group II: Antenatal women with low serum AMH levels.

Pregnant patients were checked monthly up until 28 weeks, bimonthly between 28 and 36 weeks, weekly after 36 weeks until delivery and for 7 days following delivery. Every visit during the follow-up period included taking a blood pressure reading. The ISSHP criteria were used to make the diagnosis of hypertensive illness of pregnancy.[14]

If the patient was discovered to have preeclampsia during prenatal visits, preeclampsia-specific investigations (complete blood count, peripheral smear, serum uric acid, kidney function tests, liver function tests, nonstress test, color doppler, and modified biophysical profile) were ordered. Hospital protocol was used for management of patients.

During labor, partograph monitoring was performed, and the mode of delivery was evaluated in both the hypertension and the normotensive groups. For obstetric reasons, a caesarean section was performed. They were followed during the puerperal period.

Baby's appearance, pulse, grimace, activity, and respiration (APGAR) score at 5 minutes after birth, birth weight, sex, congenital malformations, symptoms of hypoxia, meconium aspiration, and other related sequelae in both hypertensive and normotensive groups was noted.

Antenatal, intranatal, and postnatal outcomes were assessed as accidental hemorrhage, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, disseminated intravascular coagulation (DIC), preterm labor, mode of birth, indication for caesarean section and postpartum hemorrhage were investigated in mother, and neonatal outcomes as respiratory distress syndrome (RDS), intrauterine growth restriction, intrauterine death, and NICU admission were evaluated.

Comparison was made between both the groups, patients with altered (low and high) levels of AMH and normal AMH for level of significance as shown in Figure 1.

Data Analysis

The software used in study were Microsoft Excel; statistical package for the social sciences (SPSS), version 24.0; and GraphPad Prism, version 7.0. Descriptive statistics was carried out of categorical variables as frequency and percentage and continuous variables were summarized. Inferential analysis included test of significance for comparing parameters in two groups; $p < 0.05$ was considered statistically significant for assessing the association between low AMH and maternal complications. Relative risk with 95% confidence interval (CI) was calculated. Difference in means was analyzed by two independent sample *t*-tests and *p*-values less than 0.05 were statistically significant. Association was expressed in terms of relative risk (RR). A receiver operating characteristic (ROC) curve was plotted to get the reference value for Indian population.

Results

The present study was undertaken to assess the predictability of altered (low) serum AMH levels at 11–14 weeks and development of preeclampsia. A total of 350 antenatal patients were incorporated in the study and were followed up till delivery and 7 days postpartum for development of preeclampsia and for pregnancy outcomes and labor complications.

Anti-Müllerian hormone levels in antenatal patients at 11–14 weeks of gestation (normal 1.54 ng/mL to 2.66 ng/mL) and development of preeclampsia were noted, and the maternal and perinatal outcome in patients with normal and low (altered) AMH levels were analyzed and compared. A total of 60 (17%) patients had low AMH levels (<1.54 ng/mL), 290 patients (83%) had normal AMH levels and there were no patients with raised (>2.66 ng/mL) AMH levels. Mean age of patients in normal AMH group was 25.93 ± 3.94 and in Low AMH group it was 27.00 ± 3.49.

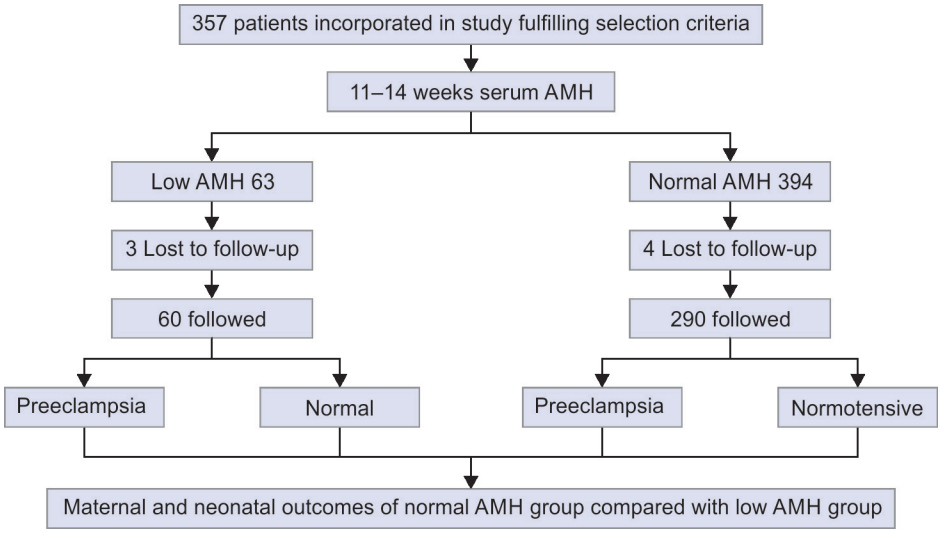

Fig. 1: Study procedure flowchart

Table 1: Distribution of patients with normal AMH and low AMH in patients with preeclampsia

	Total patients (n = 350)			
	Patients with preeclampsia (n = 58)		*Normotensive patients (n = 292)*	
11–14 weeks gestation	Patients with normal AMH (1.54–2.66)	Patients with low AMH (<1.54)	Patients with normal AMH (1.54–2.66)	Patients with low AMH (<1.54)
	20	38	270	22

Majority of the patients with normal AMH were primigravida, 151 (52.1%), and in low AMH level, 27 patients were primigravida (45%). The *p*-value ($\chi^2 = 2.594$, $p = 0.273$), using the Chi-square test, was measured and hence the groups were comparable.

There was a statistically significant difference of means for, gestational age at delivery (37.831 ± 1.870 vs 35.483 ± 2.198). Systolic blood pressure (SBP) (113.86 ± 13.405 vs 141.9 vs 3 ± 23.266), diastolic blood pressure (DBP) (73.94 ± 9.093 vs 90.00 ± 12.487), MABP (83.317 ± 10.205 vs 107.282 ± 15.701) and Birth weight at delivery (2.666 ± 1.1849 vs 2.342 ± 0.605) in patients with normal and low AMH groups with $p < 0.001$.

Of the 350 patients, 58 patients developed preeclampsia giving the frequency of 16.6% at a tertiary care center. A total of 20 patients out of 58 (34.4%) who developed preeclampsia had normal AMH levels, and the rest 38 out of 58 patients (65.6%) had low AMH levels as shown in Table 1. The frequency of preeclampsia in patients with normal AMH levels was 6.9% and the frequency of preeclampsia in patients with low AMH was 9 times more (63.3%) as compared to normal AMH levels. This association was statistically significant ($\chi^2 = 114.53$, $p < 0.001$).

Based on AMH levels at 11–14 weeks of gestation for a cutoff value of 1.54 ng/mL was derived using ROC analysis for preeclampsia. The area under the curve (AUC) was 0.7969. The new cutoff given was 1.45 ng/mL as shown in Figure 2.

Relative risk, as a measure of risk, associated with preeclampsia based on AMH levels at 11–14 weeks of gestation for a cutoff value of 1.54 derived using ROC analysis for preeclampsia. The AUC was 0.7969. As per our study results cutoff of 1.45 was recommended for Indian population from the observations. The risk of developing preeclampsia was 9.18 times more in patients with low AMH as compared to patients with normal AMH with an RR of 9.18.

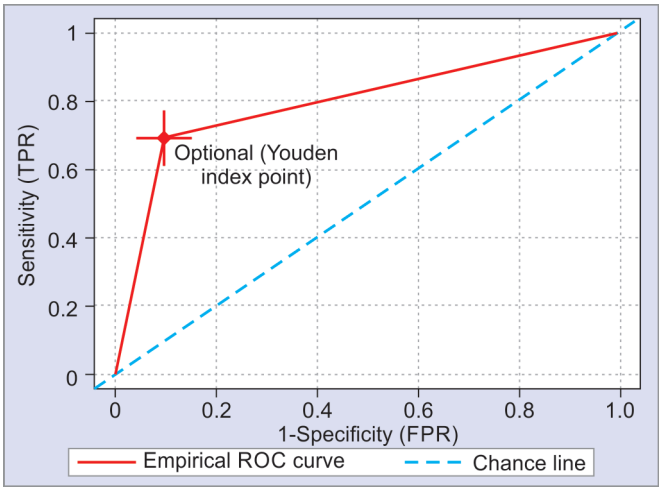

Fig. 2: The ROC plot for AMH levels at 11–14 weeks in diagnosing preeclampsia

The attributable risk in patients developing preeclampsia due to low AMHs is 52.39%. The mean AMH values at 11–14 weeks of gestation in patients with normal AMH levels were 1.996 ± 0.33153 as compared to 1.176 ± 0.18544 in patients with low AMH levels. This difference is statistically significant as the *p*-value was less than 0.001.

For preeclampsia, the sensitivity of low AMH in predicting preeclampsia is 68.9%, specificity 90.4%, positive predictive value 58.8%, and negative predictive value of 93.6% (Table 2).

The proportion of cases with LSCS in the low AMH were 35 (58.3%) as compared to 96 (33.1%) in patients with normal AMH

Table 2: Predictive evaluation of preeclampsia

Criteria	*Net sensitivity (%)*	*Net specificity (%)*	*Net PPV (%)*	*Net NPV (%)*
AMH level (11–14 weeks)	68.9	90.4	58.8	93.6

NPV, negative predictive value; PPV, positive predictive value

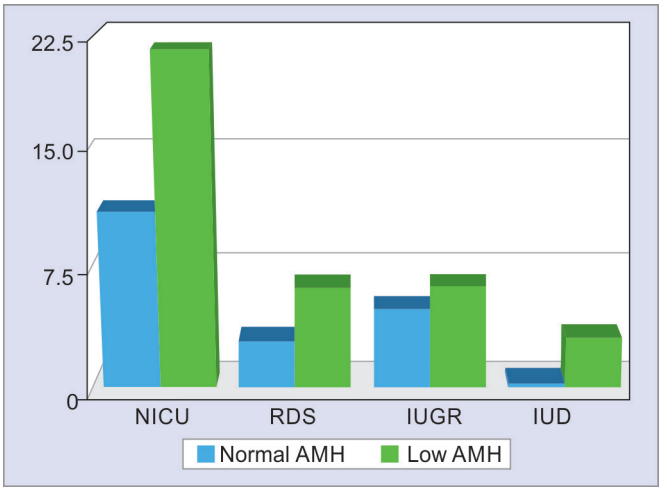

Fig. 3: Column chart showing number of patients according to fetal outcome

outcome in patients with low AMH was 6.3 times and 1.88 times more. Predictive evaluation of preeclampsia.

Discussion

In our study, maternal serum AMH was significantly lower in patients who developed preeclampsia as compared to normotensive patients. The net specificity of sequential tests suggests that the sensitivity of low AMH in predicting preeclampsia is 68.9%, specificity 90.4%, positive predictive value 58.8%, and negative predictive value of 93.6%.

As shown in Table 3, this corresponds with studies by Jamil et al.[16] (0.85 ± 1.07 vs 1.62 ± 2.29) who showed a correlation between low maternal AMH and development of preeclampsia. Mathyk et al.[12] (0.79 ± 0.40 ng/mL vs 1.45 ± 0.93 ng/mL) found statistically significant correlation ($p = 0.01$). In a study by Tokmak et al.[9] (0.62 ± 0.51 vs 0.93 ± 0.83 ng/mL), the sensitivity of AMH as predictor of preeclampsia was 67.4% and specificity was 47.7%. In study by Shand et al.[10] [4.7 (1.8–13.2) vs 5.5 (1.4–16.1) pmol/L], the levels of AMH in women developing preeclampsia were lower than normotensive women and there was 3.3-fold increase in preeclampsia when the AMH levels were below 10th percentile. In studies by Birdir et al.[13] [2.140 (1.968–2.273) vs 2.062 (1.938–2.181) ng/L] and Agabain et al.[15] [0.700 (0.225–1.500) vs 0.700 (0.400–1.275) ng/mL], they found that there was no difference and hence no association between low levels of AMH and development of preeclampsia.

Table 3: Table showing comparison of our study with different studies

Study	*Mean age*	*Type of study*	*Sample size*	*AMH levels*
Jamil et al.[16]	29.7 ± 9.1 vs 25.9 ± 5.3	Cross-sectional	20/30	0.85 ± 1.07 vs 1.62 ± 2.29
Mathyk et al.[12]	28.56 ± 6.8 vs 26.31 ± 4.04	Case–control	32/30	0.79 ± 0.40 ng/mL vs 1.45 ± 0.93 ng/mL ($p = 0.01$)
Agabain et al.[15]	27.7 ± 6.9 vs 29.5 ± 6.7	Case–control	40/40	0.700 (0.225–1.500) vs 0.700 (0.400–1.275) ng/mL
Birdir et al.[13]	32.6 (29.4–37.1) vs 31.9 (26.9–35.9)	Case–control	50/150	2.140 (1.968–2.273) vs 2.062 (1.938–2.181) ng/L
Tokmak et al.[9]	28.7 ± 6.2 vs 27.0 ± 4.2	Case–control	45/42	0.62 ± 0.51 vs 0.93 ± 0.83 ng/mL
Shand et al. [10]	NA	Retrospective cohort	11/23	4.7 (1.8–13.2) vs 4.7 (1.8–13.2) v
Our study	2.666 ± 1.1849 vs 2.342 ± 0.605	Prospective observational	60/290	1.996 ± 0.33153 vs 1.176 ± 0.18544

NA, not available

levels, which was statistically significant ($p < 0.001$). The RR of antenatal patients undergoing LSCS is 1.76 times more in patients with low AMH.

A total of 39 (13.5%) patients had preterm delivery in normal AMH group as compared to 37 (61.6%) patients with low AMH levels. This was statistically significant ($\chi^2 = 75.49$, $p < 0.001$).

The comparison of the number of occurrences revealed statistically significant difference between the two groups as indicated by $p = 0.003$ using the Chi-square test. The NICU admission cases were significantly higher 13 (21.5%) in patients with low AMH levels as compared to the 33 (11.5%) in patients with normal AMH. RDS (3.1% vs 9.96%), IUGR (5.2% vs 6.4%), meconium-stained liquor, IUD were other affections. Also, 59 (21.3%) babies had affected outcome in low AMH group as shown in Figure 3. The RR of adverse neonatal outcome in patients with low AMH levels was 1.88 times.

The risk of preeclampsia was 9.18 times with a RR of 9.18. The AMH level cutoff of 1.59 had effect on diagnosing maternal outcome as indicated by RR of 6.34. The risk of adverse maternal and neonatal

Conclusion

The study concludes that there is a definite association between low AMH levels in antenatal patients at 11–14 weeks of gestation and development of preeclampsia. The reference value of 1.45 ng/mL for AMH at 11–14 weeks of gestation is recommended for Indian population to predict preeclampsia as per our study. Low AMHs at 11–14 weeks of gestation predisposed to Preeclampsia and is associated with adverse maternal and neonatal outcome. Thus, low AMH levels at 11–14 weeks can predict preeclampsia so should be incorporated in first trimester screening.

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